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Award Number: W81XWH-10-1-0609

TITLE: Neuromimaging of Brain Injuries and Disorders at Cleveland Clinic

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REPORT DATE: October 2012

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
October 2012	Annual	23 September 2011 - 22 September 2012

4. TITLE AND SUBTITLE

Neuromimaging of Brain Injuries and Disorders at Cleveland Clinic

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0609

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Cleveland Clinic Foundation
Cleveland, OH 44195

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Blast injuries are the leading cause of injury in the Afghanistan and Iraq wars. It is unknown whether the neural and cognitive sequelae of blast-related traumatic brain injury (TBI) differs from those resulting from mechanically-induced TBI commonly observed in civilian accidents. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions. Functional MRI is an imaging method that detects increases in cerebral blood volume, flow, and oxygenation that occur locally in response to increased neuronal activity. Recent work has shown that fMRI is capable of measuring synchronous spontaneous low-frequency BOLD fluctuations (LFBFs) in the human brain during a state of alert rest. These spontaneous fluctuations are correlated in brain regions with a high degree of connectivity. The LFBF measure of functional connectivity within the brain is proving to be a powerful and sensitive measure of pathology in a number of patient populations that have previously been difficult to study with other imaging methods. We have recently demonstrated that LFBF measured functional connectivity can be combined with a structural measure of connectivity, MRI based diffusion tensor imaging/tractography, to enhance understanding of neuropathology in a patient population (Multiple Sclerosis).

15. SUBJECT TERMS

Blast-related traumatic brain injury (TBI), fMRI, DTI, cognition

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	6	19b. TELEPHONE NUMBER *(include area code)*

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Introduction

Blast injuries are the leading cause of injury in the Afghanistan and Iraq wars. In a study with Marine and Navy personnel wounded in action in Iraq during a one-month period in 2003, approximately 50% of the injuries were due to explosive devices. In an army medical facility, explosive devices and mortar were responsible for 88% of the wounded. Primary blast injuries occur when changes in atmospheric pressure cause organs containing air, such as the lung, bowel, and inner ear, to rupture. While the effects of primary blast on the brain have been considered to be the result of ruptured air emboli in blood vessels, primary blast may cause damage to the brain via other mechanisms. For example, blast to the abdomen may transfer kinetic energy from blast overpressure to the central nervous system via major blood vessels. Secondary blast injuries are caused by objects set into motion by the explosion, i.e., missiles, hitting people. Tertiary blast injuries are due to the whole body being set into motion by changes in air pressure and hitting objects. Quaternary, or miscellaneous, blast related injuries include crush injuries due to collapsed objects, burns, and smoke inhalation. TBI can result from any of these categories of blast injury. While physiological and other effects of secondary and tertiary blast injury may be similar to those in mechanical TBI due to falls or motor vehicle accidents, effects contributed by primary blast to TBI are less known, although some similarities, such as edema and oxidative stress, common to mechanical TBI have been suggested in animal models. More than 50% of blast-related TBI fall within the mild to moderate severity range.

It is unknown whether the neural and cognitive sequelae of blast-related TBI differ from those resulting from mechanically-induced TBI commonly observed in civilian accidents. The pathophysiological mechanisms associated with TBI most commonly include bleeding, direct tissue damage, and diffuse axonal injury (DAI). The presence of a penetrating injury or intracerbral hemorrhage defines the severity of a TBI as at least moderate, but DAI can occur in the milder injuries. DAI results when sudden acceleration/deceleration and angular momentum forces cause shearing or stretching of axons, which can lead to impaired axonal transport. The microscopic result is the appearance of focal axonal swellings and subsequent axonal degeneration. DAI is common after closed head injuries and most commonly affects tracts at gray/white matter junctions, particularly in the frontal and temporal regions, but is often invisible on standard structural MRI. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions. A major goal of this project is to use advanced neuroimaging techniques and computerized neuropsychological assessment to determine if the long-term (> 12 month post-injury) brain sequelae associated with blast-related mild-to-moderate TBI (MTBI) can be distinguished from sequelae associated with civilian MTBI. To our knowledge, no such study has been reported in the literature.

Body

Institutional Review Board approval

The Cleveland Clinic provided approval of the project on 12/17/2010 and the USAMRMC-ORP-HRPO on 8/29/2011.

Subject recruitment

Year two of the project was devoted to completing our target enrollment goal of 60 participants: 15 blast-related military MTBI (milTBI), 15 military controls (milCON), 15 civilian MTBI due to MVA or sports trauma (civTBI), and civilian controls with orthopedic injuries (civCON). We are happy to report that during year two, we completed enrollments of all 60 participants. Each participant underwent the comprehensive neuroimaging and neurobehavioral assessments described in the SOW and project proposal.

Key Research Accomplishments

Individual subject image analyses methods applied to resting state fcMRI and DTI data

Motor resting state fcMRI and diffusivity-based structural connectivity between primary hand motor cortices was evaluated for differences due to mechanical vs. blast TBI (milTBI, civTBI) and two control groups (milCON, civCON).

For all subjects, the fcMRI data was corrected for physiologic noise, motion and spatially filtered as described in Lowe et al. (2008). The fMRI finger tapping data was corrected for motion and spatially filtered and fitted for activation to the finger tapping paradigm and was transformed through coregistration to the connectivity data space. To account for occasional movement between scans, all scans were coregistered prior to final analysis. Functional ROIs derived from the finger tapping task were drawn on the primary motor cortices of the left and right hemispheres. Maximal activation inside the left and right primary motor cortices identified the seed and target for connectivity analysis. The fcMRI timeseries was temporally filtered below 0.1Hz and left and right primary motor connectivity was assessed through linear Pearson correlation as described in Lowe et al. (2008).

For structural connectivity, each subject's diffusion tensor imaging data was corrected for motion, eddy currents and static field warping using a new paired phase-encode spin-echo scan. The data was fitted in each voxel for tensor and diffusivity profiles. ROIs from the connectivity space and activation from fMRI scan space were transformed to DTI space and used to define seed and target ROIs for probabilistic fiber tractography, using 10 million attempts per seed voxel. Track density images were examined and diffusivity parameters for the motor pathway were integrated by track density to obtain unbiased interhemispheric motor pathway transverse diffusivity, fractional anisotropy and mean diffusivity.

The above described individual subject image analyses have been completed on all 60 enrolled subjects.

Reportable outcomes

Initial group analyses conducted on fcMRI data

A preliminary group analysis of the fcMRI data was published in abstract form at the 2012 annual conferences of the International Society for Magnetic Resonance in Medicine (ISMRM)

and the Organization of Human Brain Mapping (OHBM) (the published abstracts are included in the Appendix section). This analysis was conducted prior to completion of enrollment of all 60 subjects. The sample consisted of three groups: 9 milTBI, 13 civTBI, and 19 control subjects (milCON and civCON). For these two abstracts, a whole-brain seed-based correlation connectivity map was generated using fMRI activation and the left motor ROI and converted to t-scores as described in Lowe et al. (2008). The correlation map was corrected for global bias by performing an approximate z-transform, by normalizing the mean and standard deviation of the whole-brain t-score distribution. The z-score maps were transformed into standard stereotaxic (Talairach) space and compared between TBI and control groups and between TBI blast and non-blast groups by ANOVA.

Results of this preliminary analysis of fcMRI data indicate that functional connectivity to left primary motor cortex in TBI participants (see Figure 1a in abstracts located in appendices) and controls (Figure 1b) is preserved in cortical primary motor, premotor, supplementary motor areas, but connectivity to the visual cortex, an area with strong synchronous BOLD fluctuations with primary motor cortex at rest, is greatly reduced in TBI compared to controls. Figure 1c shows the difference between the blast TBI (milTBI) and non-blast TBI (civTBI) groups, showing a distinct increase in medial thalamic connectivity in blast versus non-blast TBI. These preliminary results suggest that blast TBI produces a unique effect on functional connectivity patterns that can be distinguished from non-blast TBI.

Conclusion

Our preliminary group analysis conducted on a subset of our sample suggests difference in motor cortex functional connectivity between TBI and controls and between blast and non-blast TBI. During the next funding year, we will complete group analyses of the entire sample for both the fcMRI and DTI datasets. Results of these data analyses will be reported in published in scientific journals and presented at scientific meetings.

References

Lowe MJ, (2008) Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. *Human Brain Mapping, 29*, 818-827.

Appendices

1. Abstract presented at the 2012 annual conference of the International Society for Magnetic Resonance in Medicine (ISMRM)

2. Abstract presented at the 2012 annual conference of the Organization of Human Brain Mapping (OHBM)